PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/043696	23.12.2004	23.12.2003

International Patent Classification (IPC) or both national classification and IPC
C12N5/06, C12N5/08

Applicant
NOVOCELL, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/043696

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	18-61,63-73
	No:	Claims	1-17,62,74,75
Inventive step (IS)	Yes:	Claims	36-61,63-72
	No:	Claims	20-35,73
Industrial applicability (IA)	Yes:	Claims	1-75
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. Reasoned statement (Continuation)

1 CITATIONS

Reference is made to the following documents:

D1: SCHULDINER MAYA ET AL: "Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 97, no. 21, 10 October 2000 (2000-10-10), pages 11307-11312

D2: KUBO A ET AL: "Development of definitive endoderm from embryonic stem cells in culture" DEVELOPMENT, COMPANY OF BIOLOGISTS, CAMBRIDGE,, GB, vol. 131, no. 7, April 2004 (2004-04), pages 1651-1662,

D3: WO 2004/098490 A (MOUNT SINAI SCHOOL OF MEDICINE OF NEW YORK UNIVERSITY; KELLER, GORDON,) 18 November 2004 (2004-11-18)

2 NOVELTY (Art. 33(2) PCT)

2.1 D1 discloses the differentiation of human embryonic stem cells by treatment with NGF and HGF to cells of the three embryonic layer, including endodermal cells. In this way D2 discloses a cell culture comprising human endoderm cells and although D2 does not disclose the expression of the markers mentioned in claims 4-13, the cell culture is considered not to be different form the cell cultures of claims 2-13. In view of D1, the subject matter of claims 1-17,74,75 is not considered to be novel.

2.2 Claim 62 for a product defined in terms of a process of manufacture is admissible only if the products as such fulfill the requirements of patentability, i.e. inter alia that they are novel and inventive. A product is not rendered novel merely by the fact that it is produced by means of a new process (see Guidelines CIII 4.7b). However, the cell

of claim 62 is disclosed in D1 and therefore, claim 62 is not considered to be novel.

2.3 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-17,62,74,75 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

3 INVENTIVE STEP (Art. 33(3) PCT)

3.1 For inventive step analysis of claim 20, Document D1 is considered to represent the most relevant state of the art and discloses a cell culture comprising human definitive endodermal cells. The subject-matter of claim 20 differs in that a cell population comprising at least 90% of human definitive endodermal cells.

3.2 The problem to be solved by the subject matter of claim 20 may therefore be regarded as the provision of an more purified cell population comprising human definitive endodermal cells. The solution would be a cell population comprising at least 90% of human definitive endodermal cells.

3.3 This solution cannot however be considered as involving an inventive step (Article 33(3) PCT) because it would be obvious for the skilled person to obtain the cell population of claim 20, starting from the cell culture of D1 and purifying the definitive endodermal cells using endodermal cell markers known in the art.

3.4 Claims 18,19, 21-35 and claim 73 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step.

3.5 For inventive step analysis of claim 36, D1 is considered to represent the most relevant state of the art and discloses a method to produce human endodermal cells comprising treatment of embryonic stem cells with NGF or HGF. The subject-matter of claim 36 differs in that a method for producing definitive endoderm cells is claimed comprising treatment of pluripotent cells with a growth factor of the TGFβ

superfamily.

3.6 The problem to be solved by the subject matter of claim 36 may therefore be regarded as the provision of an alternative method to produce human endodermal cells. The solution would be a method for producing definitive endoderm cells comprising treatment of pluripotent cells with a growth factor of the TGFβ superfamily.

3.7 This solution is considered as involving an inventive step (Article 33(3) PCT) because it would not be obvious for the skilled person to treat pluripotent cells with a growth factor of the TGFβ superfamily to produce definitive endodermal cells.

3.8 Consequently, also claims 37-61,63-72 are considered to be inventive.

3.9 The present application does not satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims 1-35,62,73-75 does not involve an inventive step (Rule 65(1)(2) PCT). The subject-matter of claims 36-61,63-72 is considered to involve an inventive step.

VI. Certain documents cited (Continuation)

7 Certain published documents :

	Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
7.1	2004/098490	18.12.2004	19.05.2003	17.05.2002 04.02.2003

7.2 KUBO A ET AL: "Development of definitive endoderm from embryonic stem cells in

culture" DEVELOPMENT, COMPANY OF BIOLOGISTS, CAMBRIDGE,, GB, vol. 131, no. 7, April 2004 (2004-04), pages 1651-1662, XP002985523 ISSN: 0950-1991

7.3 Although D2 and D3 do not constitute prior art within the meaning of Rule 64.1(b), it appears to disclose all the features of certain claims of the present application. It might therefore be taken into consideration in the regional phase before the EPO. No check has been made as to wether the priority of this application has been validly claimed.

VIII. Certain Observations (Continuation)

8 The application does not meet the requirements of Article 6 PCT because claims are not clear for the following reasons:

8.1 The term "about" used in claims 1-3,14,20-22,33,37-40,53-58,68,69 is vague and indefinite and as such renders the scope of the claims unclear; accordingly, the claims require amendment to remove this defect (Art. 6 PCT).

8.2 The abbreviations of the markers should be explained in the claims to fulfill the requirements of Art. 6 PCT.

8.3 Claims 63 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempts to define the subject-matter in terms of the result to be achieved, namely "differentiating cells in a population of pluripotent human cells so as to produce definitive endoderm cells", which merely amounts to a statement of the underlying problem,. The technical features necessary for achieving this result are however missing. Therefore, the features of claim 64 should be incorporated in claim 63, since the treatment with a growth factor of the TGFβ superfamily seems to be an essential technical feature of the present application.

8.4 The expressions "in an amount sufficient to promote differentiation" used in claims 36

and 64 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

9 The applicant is hereby informed that under the EPC the use of human embryonic cells for industrial or commercial purposes is excluded from patentability (Art. 563(a) EPC and Rule 23d(c) EPC).